



Blood-brain Barrier Disruption: Applications and Advantages Presentation to CMS

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Abbreviations

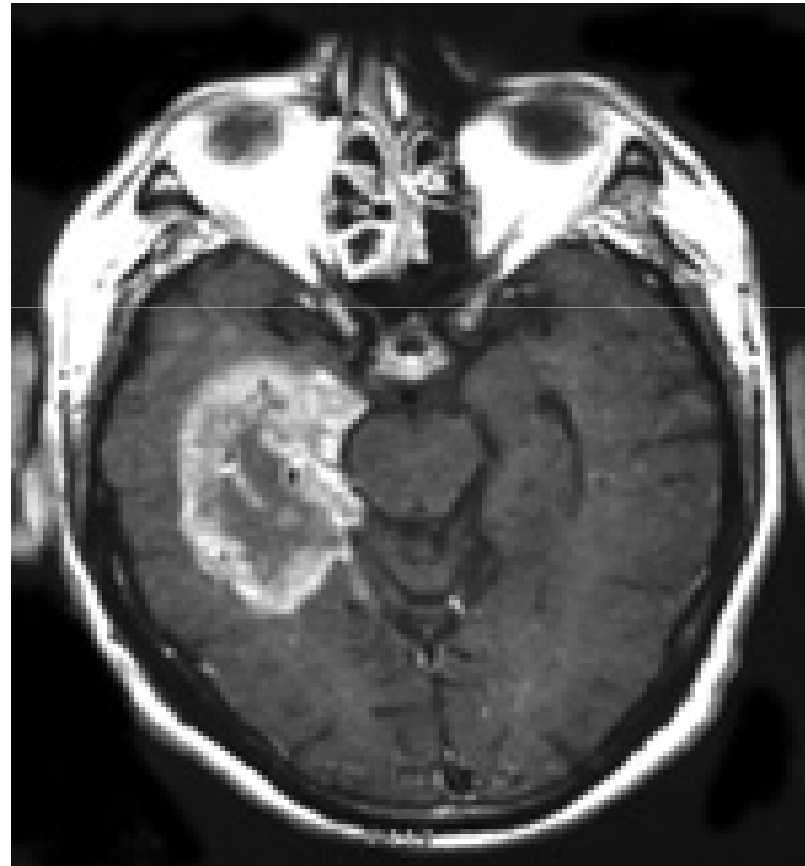
- **BBB – blood-brain barrier**
- **BBBD – blood-brain barrier disruption**
- **IA/BBBD – intra-arterial chemo with BBBD**
- **CNS – central nervous system**
- **PCNSL – primary CNS lymphoma**
- **RT – radiation therapy**
- **IV – intravenous**

Take home messages

- **BBBD is a uniquely useful option for delivery of medicines to the brain for treatment of patients with brain cancer**
- **Treatment of patients with PCNSL using BBBD affords long term survival without the need for radiation therapy.**
- **BBBD can avoid the long term cognitive effects of radiation therapy**
- **BBBD offers the possibility of delivering important drugs to the brain such as rituximab, trastuzumab, antibodies or genes**

Brain Cancer

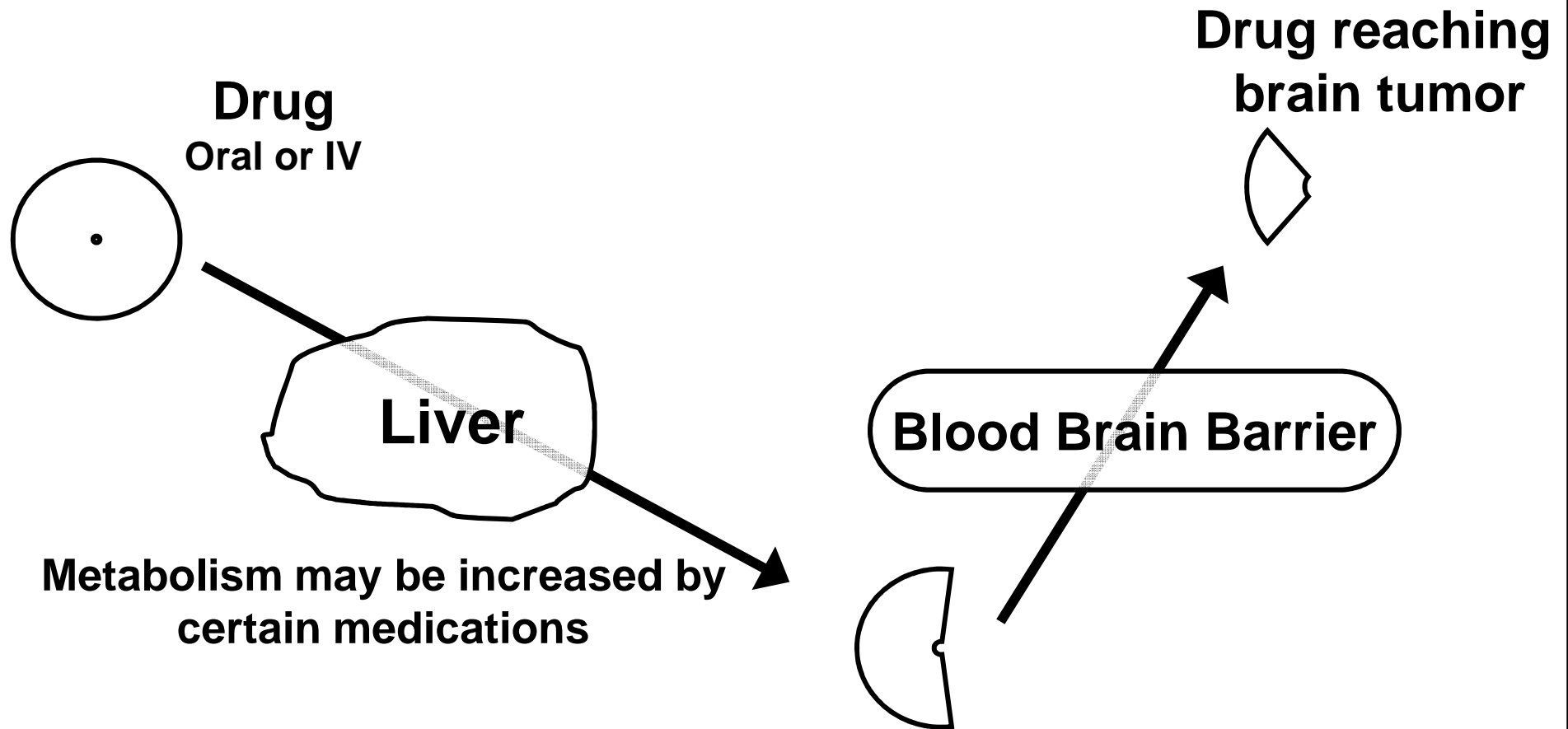
- **Approx 200,000 patients per year**
- **~ 150,000+ deaths**
- **Primary tumors and brain metastases**
- **Chemotherapy can improve survival**
- **Often younger patients**
- **A leading cause of cancer death in children**



Burden of brain cancer

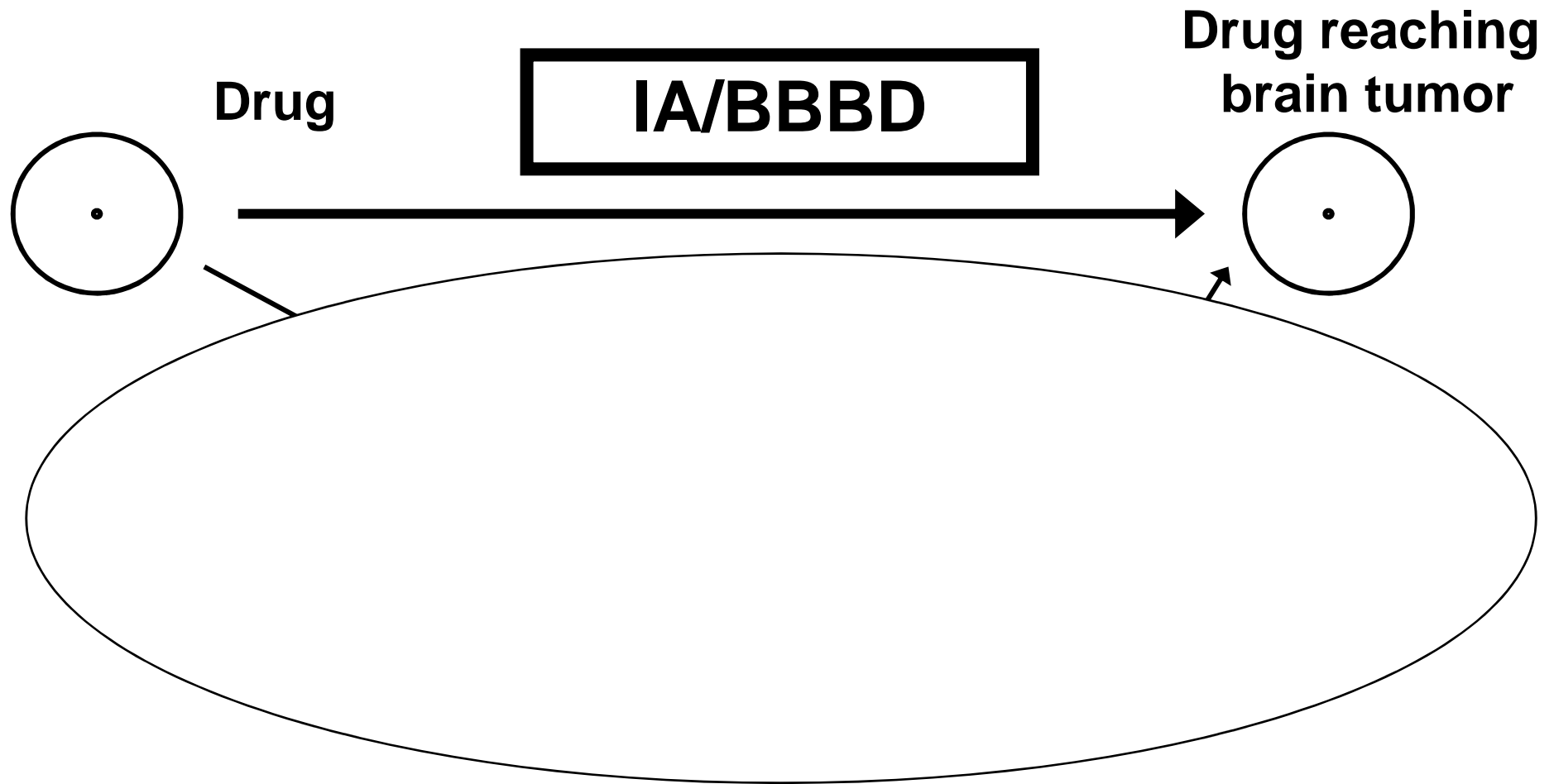
- **Personality changes**
- **Loss of communication – speech impairment**
- **Loss of motor function**
- **Vision loss**
- **Seizures**
- **Loss of independence**
- **Stress on caregivers – high rate of divorce**
- **Complicated by need for steroids**

Delivery of Drug to the Brain Tumor



Courtesy Stuart Grossman

Delivery of Drug to the Brain Tumor



Adapted from Stuart Grossman

Drug delivery to the brain

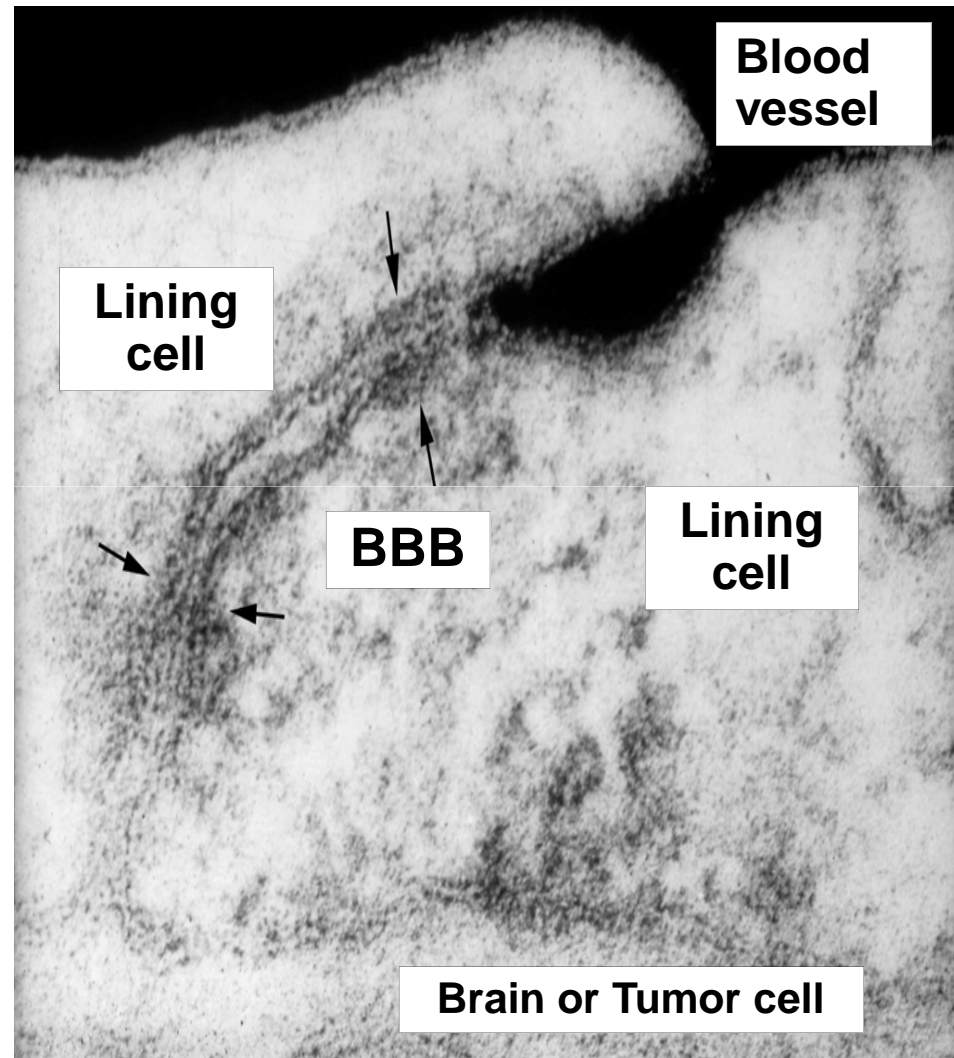
- **Major limitation of chemotherapy for brain tumors**
- **After passing through the liver, most chemotherapy drugs do not reach brain tumor**

Why?

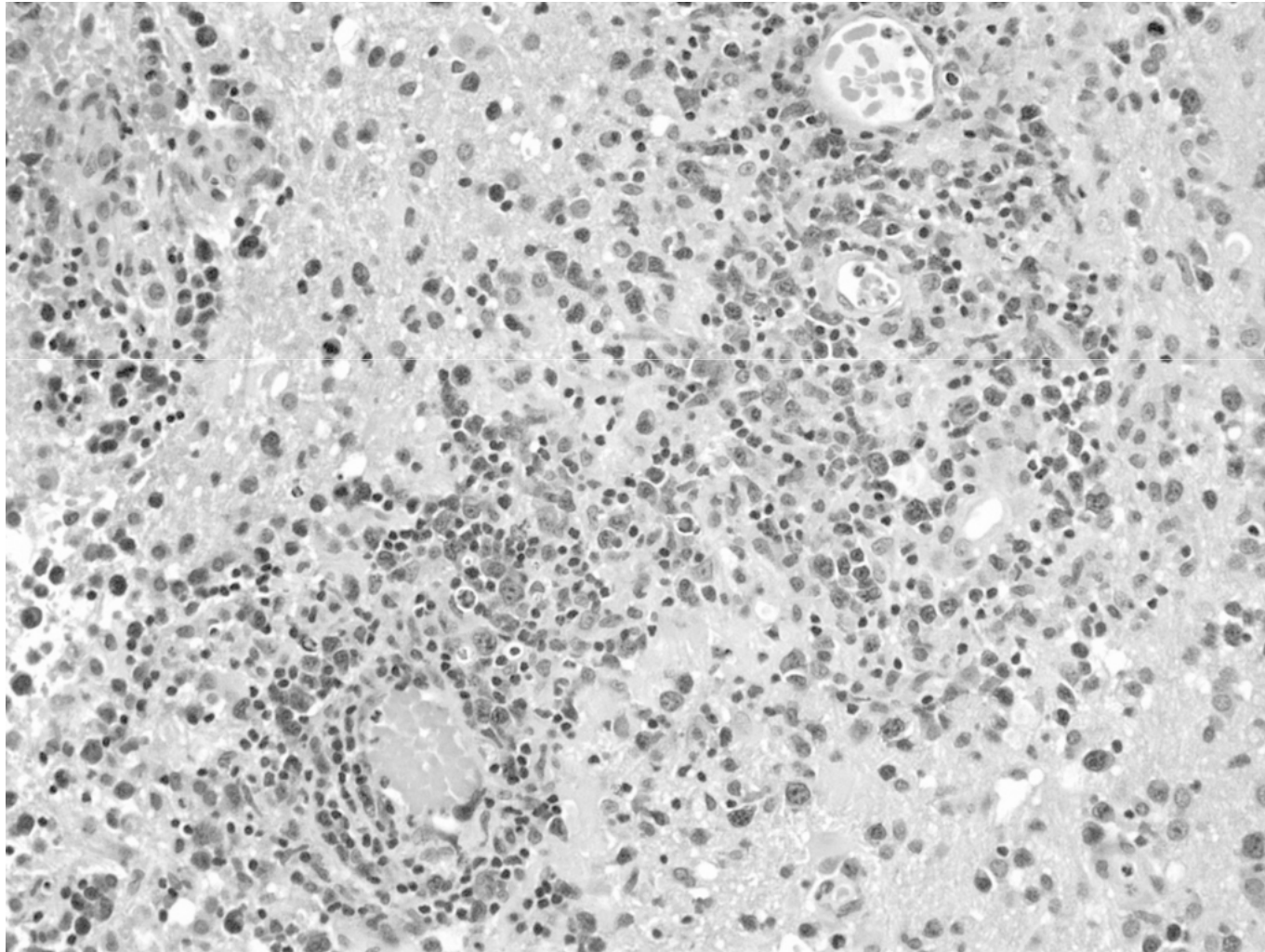
The blood-brain barrier

Blood-brain barrier

- Protects brain from toxins
- Prevents entry of most drugs into the brain



Primary CNS Lymphoma

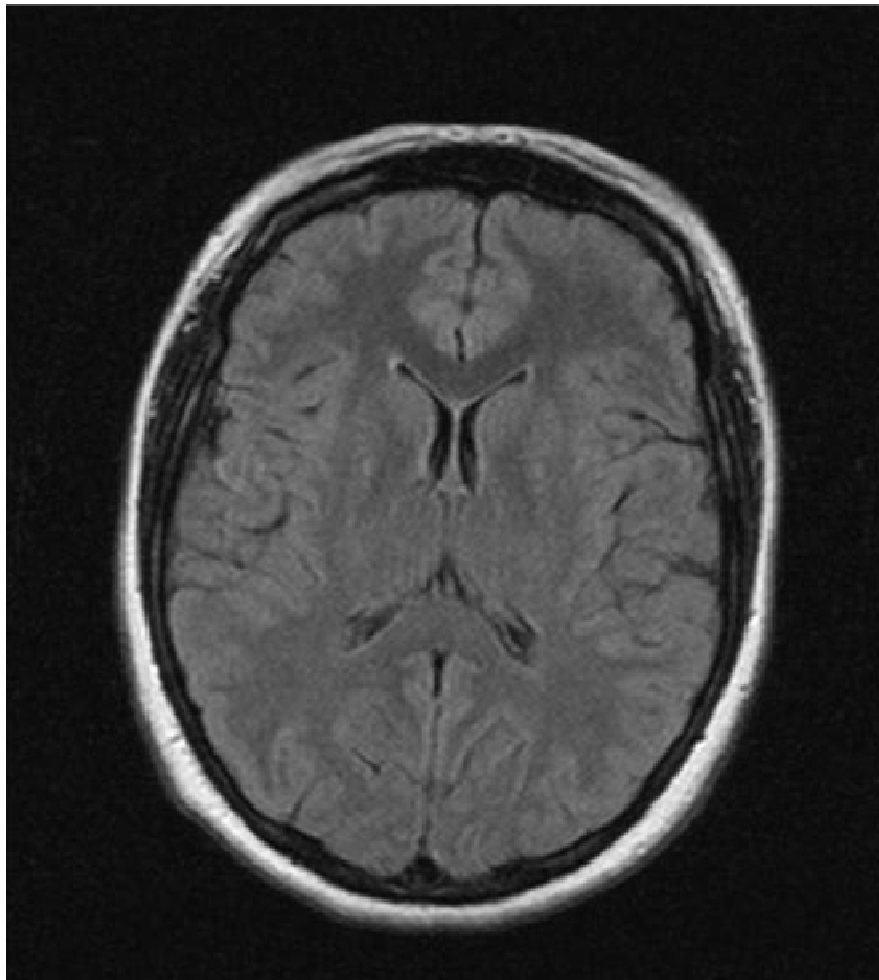


**An unmet need:
Getting drugs to the brain
tumor**

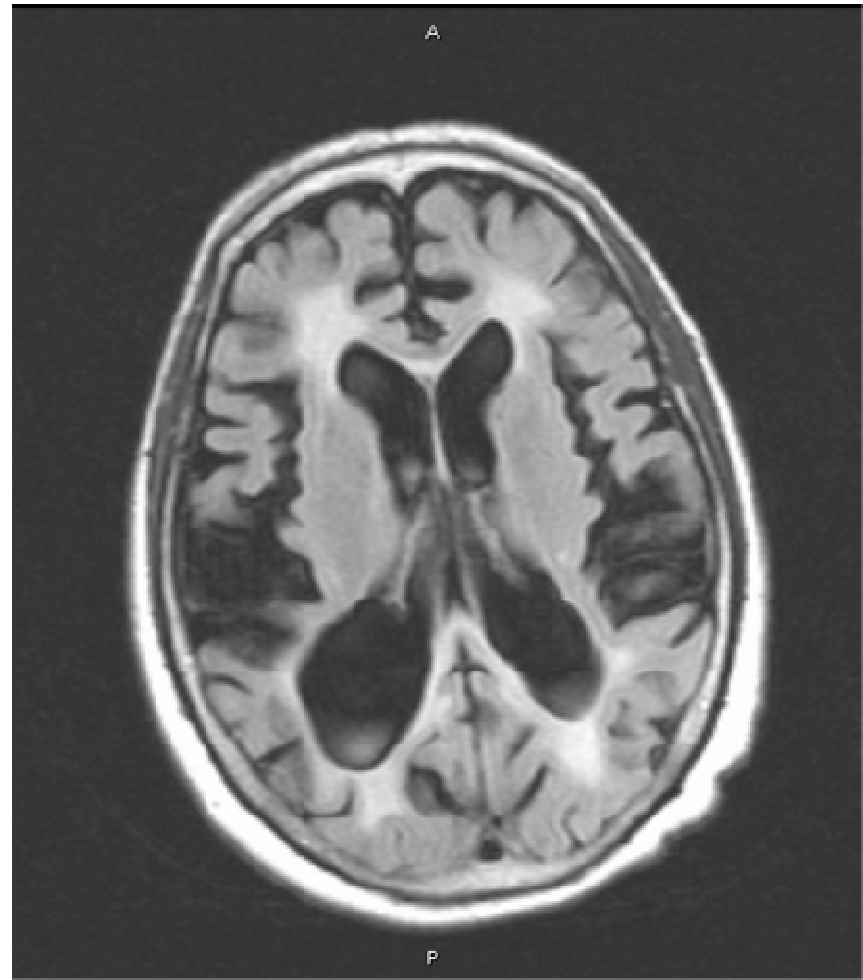
Strategy to optimize drug delivery to tumor

- **Blood brain barrier disruption (BBBD)**
- **Developed out of need for better drug delivery**
- **Advantages:**
 - **Ability to deliver 10 – 100 times as much chemotherapy to the tumor (c/w IV or oral)**
 - **Potential to deliver large molecules to brain**
 - **Rituximab (Rituxan™) for CNS lymphoma**
 - **Trastuzumab (Herceptin™) for breast cancer**
- **Avoid need for radiation therapy**

Long term affect of combined chemo-radiation therapy

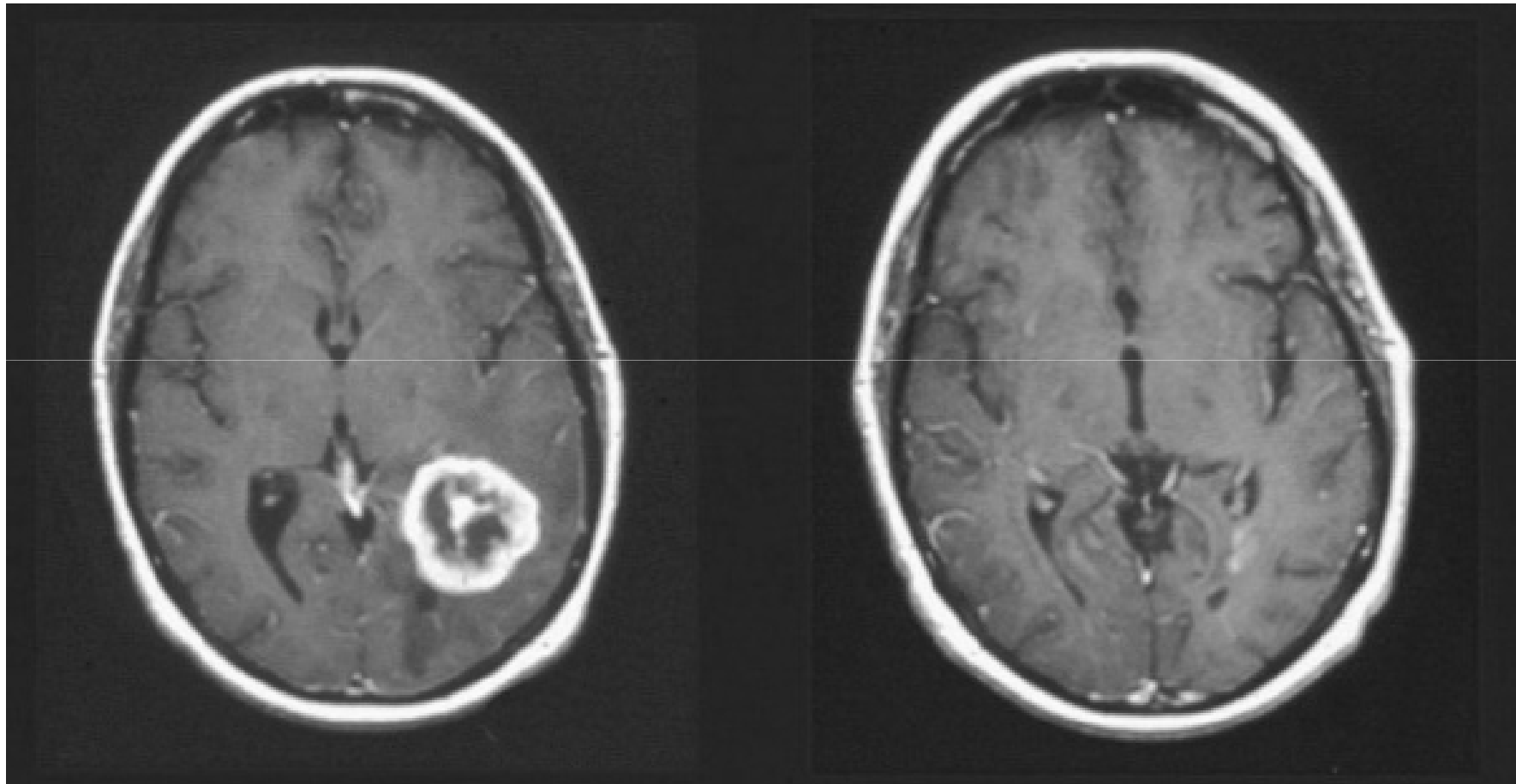


normal



after radiation

Metastatic Ovarian Cancer before & after IA/BBBD



Courtesy Edward Neuwelt

Intra-arterial chemo/BBB disruption (IA/BBBD)

- **Systemic toxicity limits dose of IV chemotherapy that can be given**
- **IA tx + BBBD ↑ drug delivery to brain tumor by ~ 10-100 times**
- **Most useful for patients with chemotherapy-sensitive cancers such as CNS lymphoma, brain metastases from breast cancer, testicular cancer**

BBBD improves drug delivery to tumor and brain around tumor

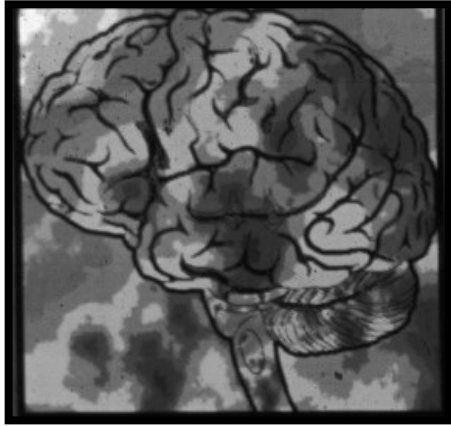
MTX Concentration (ng/g)

	<u>CONTROL</u>		<u>OPEN BARRIER</u>	
	IV	IC	IV	IC
TUMOR	530	923	843	2275
BAT	138	316	784	2631

IV = intravenous

IC = intracarotid

BAT = brain around tumor



Sequencing of BBBD Chemotherapy and Radiotherapy

Effect on Drug Delivery

<i>Treatment</i>	<i>Methotrexate delivery to rat brain*</i>
Radiation 30 days before BBBD	$12.9 \pm 3.1, n = 4$
No radiation	$28.8 \pm 5.7, n = 4$

****Disrupted right hemisphere compared to nondisrupted left hemisphere***

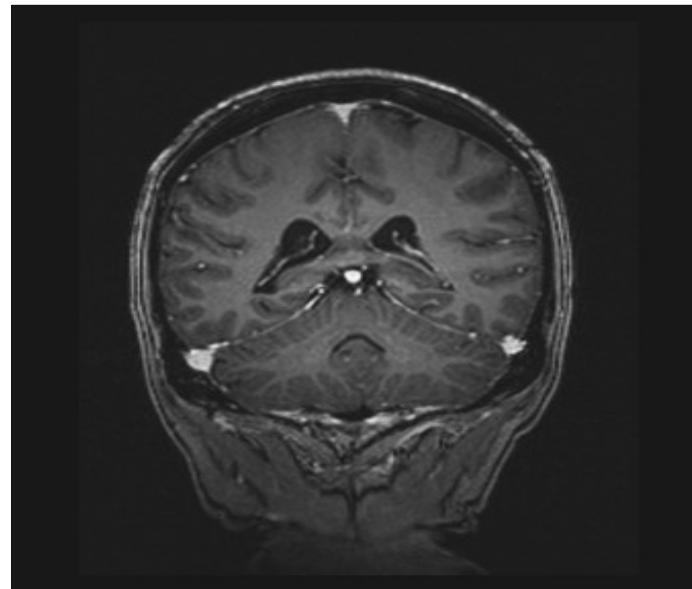
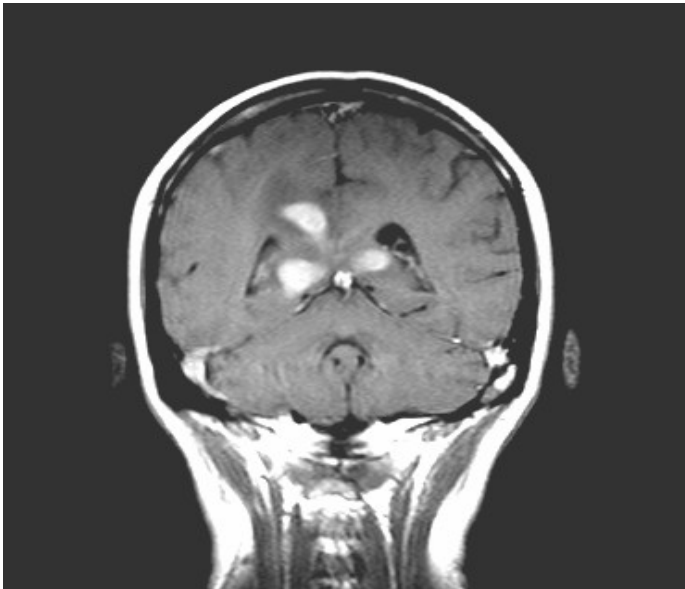
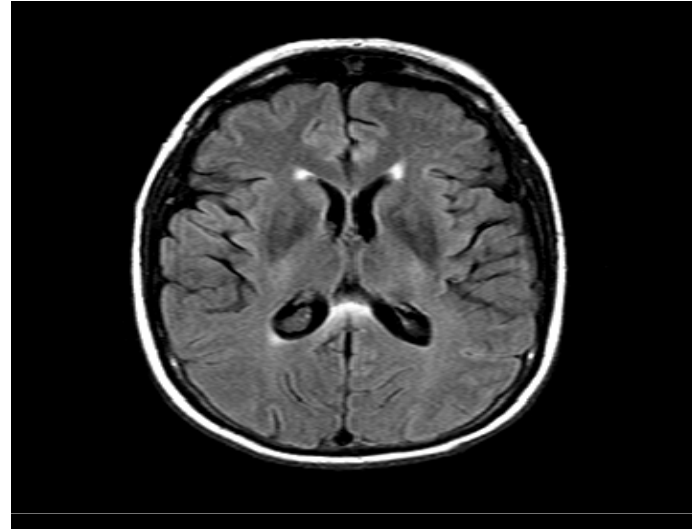
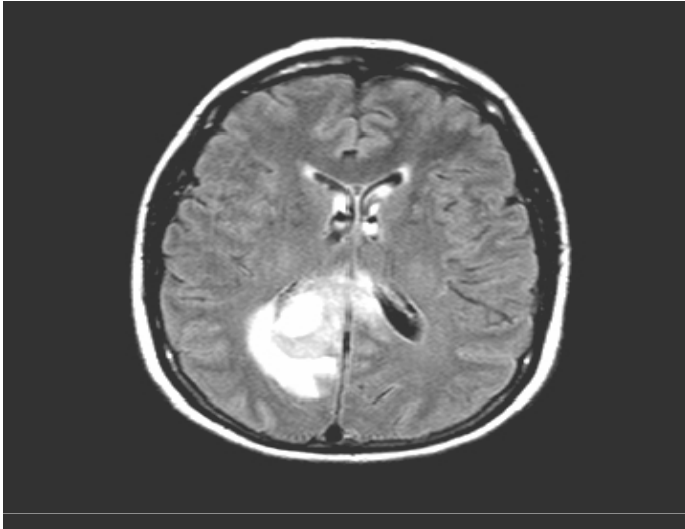
Less cognitive toxicity

- **Example, primary CNS lymphoma**
- **5 yr survival 42% with no radiation therapy (RT) and no cognitive loss¹**
- **compares with same survival but 32% dementia with combined chemo + RT²**

¹*McAllister, Neurosurgery, 46:51, 2000*

²*Abrey, J Clin Oncol 16:859, 1998*

CNS Lymphoma after IA/BBBD



Courtesy Lilyana Angelov

Study	Patients (n)	Previously Tx	RR (CR+PR)	Median PFS (mos)	OS (mos)
RTOG 93-10 <i>HD Mtx + WBXRT</i>	102	No	94 %	24	36.9
EORTC 20962 <i>HD Mtx + WBXRT</i>	52 (< 65 y.o.)	No	81 %	---	46
EORTC 26952 <i>HD Mtx + Chemo</i>	50 (> 60 y.o.)	No	48 %	10.6	14.3
NABTT 96-07 <i>HD Mtx + Chemo</i>	25	No	74 %	12.8	23+
BBBD	74	No	84 %	---	40.7

Blood-brain barrier disruption

How it's done

- **Inpatient procedure**
- **Patient placed under general anesthesia; anti-seizure meds given to patient to prevent seizures**
- **Catheter placed in artery in groin (femoral artery)**
- **Catheter advanced into arteries that lead to brain (carotid or vertebral artery)**

Blood-brain barrier disruption

How it's done

- **Mannitol infused into catheter to open (disrupt) BBB**
- **Drug infused through same catheter to deliver maximum concentration to tumor**
- **Angiogram done to make sure artery not damaged**

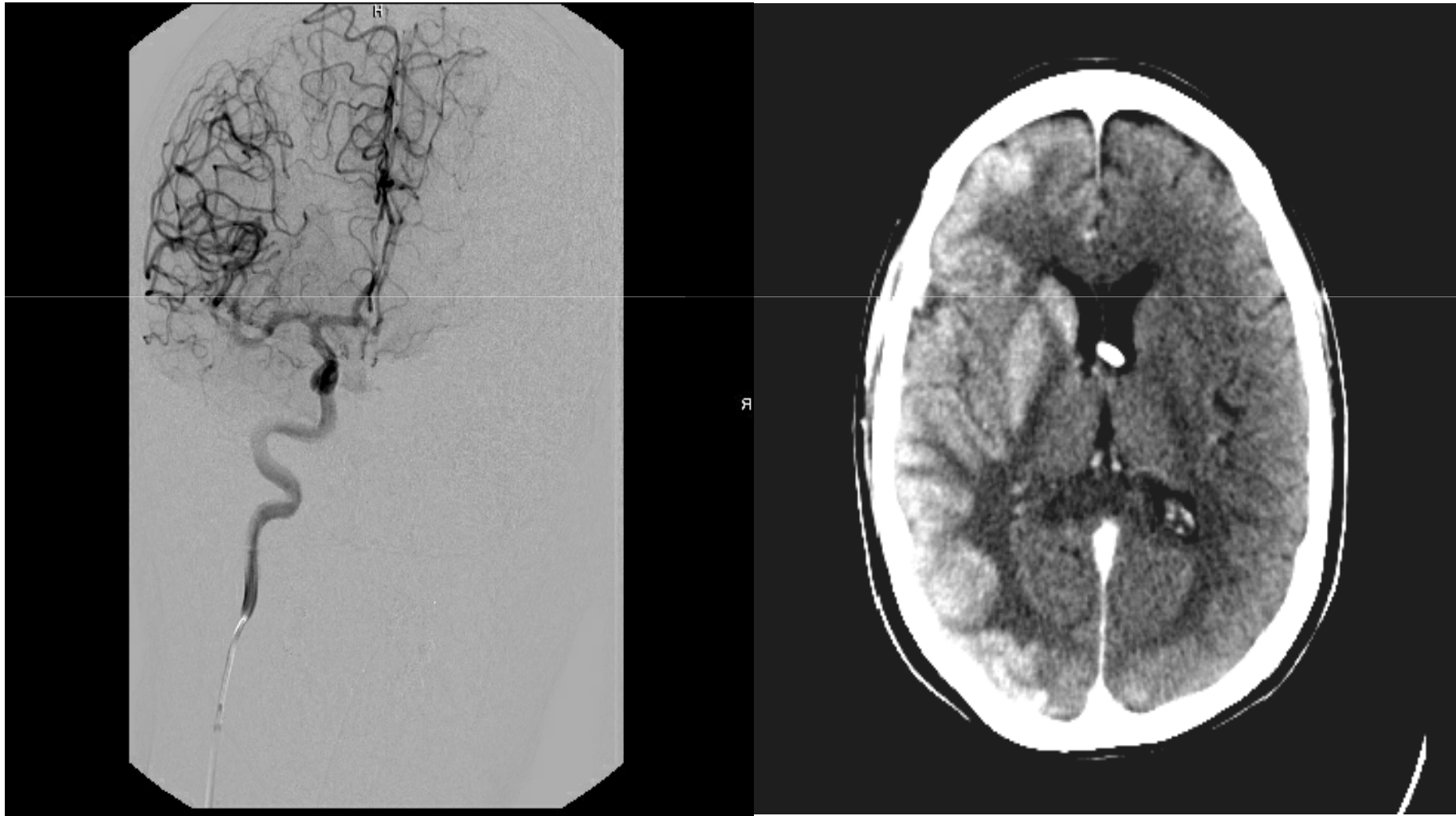
Blood-brain barrier disruption

How it's done

- **Patient taken to recovery room**
- **BBB closes few hours later**
- **Procedure repeated next day using a different artery**
- **Patient leaves hospital day 4**

Blood-brain barrier disruption

Carotid artery



Possible risks

- **Comparable to those seen with standard chemotherapy**
- **Procedural risks**
 - **general anesthesia**
 - **damage to artery**
 - **these are rare; much less common than neurotoxicity due to radiation therapy**

BBBD PARTICIPANTS



BBBD

Potential future uses

- **Delivery of larger substances to brain**
- **Antibodies for treatment of lymphoma, breast cancer**
- **Modified viruses that will deliver genes for gene therapy**
- **Drugs for treatment of other CNS diseases - ?Alzheimer's disease**

BBBD

Potential future uses

- **Clinical trials in progress or starting**
 - **PCNSL: Rituximab + chemotherapy**
 - **High grade glioma: Chemotherapy + STS**
 - **Brain metastases from breast cancer: Trastuzumab + chemotherapy**
 - **Pediatric brain tumors: chemotherapy + NAC**
- STS = sodium thiosulfate – protects against bone marrow and hearing side effects
- NAC = N-acetyl cysteine – protects bone marrow against side effects

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Thank you!